UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/855,342	05/14/2001	Michael A. Caligiuri	35784/209112 (5784-50)	8842

20855 7590 11/21/2006

ROBINS & PASTERNAK
1731 EMBARCADERO ROAD
SUITE 230
PALO ALTO, CA 94303

EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 11/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/855,342	CALIGIURI ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-50,52,53,55,56,58,59 and 61-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-50,52,53,55,56,58,59 and 61-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed September 1, 2006, is acknowledged and has been entered. Claims 51, 54, 57, and 60 have been canceled. Claims 12, 16, 17, 28, 42, 52, 55, 58, 61, 63, 71, and 72 have been amended. Claims 74-79 have been added.

2. The declaration under 37 C.F.R. § 1.132 by Michael Caligiuri, Neal Meropol, and Robert Schlisky filed September 6, 2006, is acknowledged and has been entered.

3. Claims 12-50, 52, 53, 55, 56, 58, 59, and 61-79 are pending in the application and are currently under prosecution.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. The following Office action contains NEW GROUNDS of rejection necessitated by amendment.

Response to Amendment

6. The amendment filed on September 1, 2006, is considered non-compliant because it fails to meet the requirements of 37 CFR § 1.121, as amended on June 30, 2003 (see *68 Fed. Reg. 38611*, Jun. 30, 2003).

In the interest of advancing prosecution, and in lieu of mailing a Notice of Non-Compliant Amendment, Applicant is reminded to adhere to the requirements set forth under 37 CFR § 1.121, as amended on June 30, 2003 (see *68 Fed. Reg. 38611*, Jun. 30, 2003).

The amendment filed on September 1, 2006, is not compliant because, while claim 60 has been canceled, the text of the canceled claim has been included in the listing of claims.

Briefly, the amendment practice requires a listing of all claims beginning on a separate sheet. Each claim ever presented must be included in the listing of claims together with a single proper status identifier in parentheses. The permissible status identifiers include: "original", "currently amended", "canceled", "withdrawn", "previously presented", "new", and "not entered". The text of all pending claims, including withdrawn claims, must be presented. Markings to show only the changes made in the current amendment relative to the immediate prior version should be included with the text of all currently amended claims, including withdrawn claims that are amended. Added text must be shown by underlining the added text. Generally deleted text must be shown by strikethrough (e.g., ~~strikethrough~~); or if the strikethrough cannot be easily perceived, and for deletion of five or fewer characters, the deleted text may be marked by the inclusion of deleted text in double brackets (e.g., [[444]]). **The text of "canceled" and "not entered" claims must not be presented**; and consecutive "canceled" or "not entered" claims may be grouped together in one line (e.g., Claims 1-11 (canceled); Claims 51-62 (not entered)).

Only the corrected section of the non-compliant amendment must be resubmitted (in its entirety), e.g., the entire "Amendments to the claims" section of applicant's amendment must be re-submitted. 37 CFR § 1.121(h).

7. The amendment filed September 1, 2006, is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material, which appears not supported by the original disclosure, is the reference to "SEQ ID NO: 1" that has been inserted by the amendment to the specification at page 29, and the Sequence Listing disclosing the amino acid sequence of SEQ ID NO: 1.

As amended at page 29 in the paragraph beginning in line 2, the specification reads:

> The IL-2 formulation in this study is manufactured by Chrion Corporation of Emeryville, California, under the tradename Proleukin. The IL-2 in this formulation is a recombinantly produced human IL-2 mutein, called aldesleukin, which differs from the native human IL-2 sequence (SEQ ID NO:1) in having the initial alanine residue

> eliminated and the cysteine residue at position 125 replaced by serine (referred to as des-alanyl-1, serine-125 human interleukin-2). This IL-2 mutein is expressed from E. coli, and subsequently purified by diafiltration and cation exchange chromatography as described in U.S. Patent No. 4,931,543.

Thus, the introduction of SEQ ID NO: 1 at page 29 by the amendment defines the native human IL-2 sequence as the amino acid sequence set forth as SEQ ID NO: 1. Notably, the original disclosure at page 29 provides no apparent nexus between the amino acid sequence set forth as SEQ ID NO: 1 and the amino acid sequence of native human IL-2.

At page 15, paragraph 2, of the amendment filed September 1, 2006, Applicant has asserted that the specification, as originally filed, provides support for this amendment to the specification, since "SEQ ID NO:1 now corresponds to the sequence of native mature human IL-2 disclosed in Figure 2b of U.S. Patent No. 4,738,927, which was cited in the instant application, for example, at page 17, line 13, and incorporated by reference".

The disclosure at page 17, lines 1-14, of the specification reads as follows:

> The IL-2 or variants thereof for use in the methods of the present invention may be from any source, but preferably is recombinant IL-2. By "recombinant IL-2" is intended interleukin-2 that has comparable biological activity to native-sequence IL-2 and that has been prepared by recombinant DNA techniques as described, for example, by Taniguchi et al. (1983) Nature 302:305-310 and Devos (1983) Nucleic Acids Research 11:4307-4323 or mutationally altered IL-2 as described by Wang et al. (1984) Science 224:1431-1433. In general, the gene coding for IL-2 is cloned and then expressed in transformed organisms, preferably a microorganism, and most preferably E. coli, as described herein. The host organism expresses the foreign gene to produce IL-2 under expression conditions. Synthetic recombinant IL-2 can also be made in eukaryotes, such as yeast or human cells. Processes for growing, harvesting, disrupting, or extracting the IL-2 from cells are substantially described in, for example, U.S. Pat. Nos. 4,604,377; 4,738,927; 4,656,132; 4,569,790; 4,748,234; 4,530,787; 4,572,798; 4,748,234; and 4,931,543, herein incorporated by reference in their entireties.

Agreeably, the specification, as filed, refers to U.S. Patent No. 4,738,927, at page 17, lines 10-14, but nowhere else; and agreeably the patent has been incorporated by reference in its entirety, together with the entireties of each of U.S. Pat. Nos. 4,604,377; 4,656,132; 4,569,790; 4,748,234; 4,530,787; 4,572,798; 4,748,234; and 4,931,543.

This disclosure, however, does not appear to provide a nexus between the amino acid sequence set forth as the corresponding amino acid sequence depicted in Figure 2B of U.S. Patent No. 4,738,927 (i.e., SEQ ID NO: 1) and the amino acid sequence of native human IL-2.

Figure 2B of U.S. Patent No. 4,738,927 depicts three distinct amino acid sequences, which are designated "Amino Acid Sequence 1", "Amino Acid Sequence 2", and "Amino Acid Sequence 3", and which, according to the corresponding brief description of the figure (column 3, lines 16-19), are the amino acid sequences of "the polypeptides which possess IL-2 activity".

Figure 2B of U.S. Patent No. 4,738,927 does not describe any one of the three amino acid sequences as the sequence of the native human IL-2 molecule.

Accordingly, contrary to Applicant's contention, the disclosure at page 17 of the specification does not appear to provide support for the added material because it does not *particularly* identify that added material, not as that contained by the disclosure of U.S. Patent No. 4,738,927, per se, and not as any particular part thereof.

According to M.P.E.P. 608.01(p):

> Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. *In re de Seversky*, 474 F.2d 671, 177 USPQ 144 (CCPA 1973).

With regard to incorporation by reference, the Federal Circuit in deciding *Advanced Display Systems Inc. v. Kent State University,* 54 USPQ2d 1673 (CA FC), has further opined:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USPQ 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents. *See In re Seversky,* 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-03, 170 USPQ 213, 216-17 (CCPA 1971)

> (reasoning that a rejection for anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order have that material considered part of a later application); *cf. Lund*, 376 F.2d at 989, 153 USPQ at 631 (holding that a one sentence reference to an abandoned application is not sufficient to incorporate material from the abandoned application into a new application). Whether and to what extent material has been incorporated by reference into a host document is a question of law. *See Quaker City Gear Works, Inc. v. Skil Corp.*, 747 F.2d 1446, 1453-54, 223 USPQ 1161, 1166 (Fed. Cir. 1984) (reasoning that whether a document is incorporated by reference into a patent presents a question of law when determining enablement). *Id.* at 1679-1680.
>
> [Thus] the standard of one reasonably skilled in the art should be used to determine whether the host document describes the material to be incorporated by reference with sufficient particularity. *Id.* at 1680.

In this instance, the disclosure at page 17 of the specification does not provide proper written support for the added material since that material is a particular amino acid sequence disclosed as one of three in a figure in one of several patents, which is incorporated by reference but not particularly referred to as providing a disclosure of the particular amino acid sequence, which Applicant has alleged is the amino acid sequence of native mature human IL-2.

Applicant's remarks at pages 16 and 17 of the amendment, addressing the proscription against the introduction of new matter in a patent application, are acknowledged. Applicant has further remarked the sequence of human IL-2 was well known in the art at the time the application was filed, as it was disclosed in Figure 2B of U.S. Patent No. 4,738,927, which has been incorporated in this application by reference in its entirety. Applicant's remarks have been carefully considered but not found persuasive, since, as explained above, the disclosure incorporating U.S. Patent No. 4,738,927 by reference would not lead one to the particular amino acid sequence, which has been added to the instant specification by the amendment.

Accordingly, Applicant is required to cancel the new matter in the reply to this Office Action, or otherwise explain why the statement of incorporation by reference of U.S. Patent No. 4,738,927 A at page 17 of the specification should be regarded as identifying with the requisite detailed particularity the specific material, which has been added.

Response to Declaration under 37 C.F.R. § 1.132

8. The merit of the declaration under 37 C.F.R. § 1.132 by Michael Caligiuri, Neal Meropol, and Robert Schlisky, which was filed September 6, 2006, has been carefully considered but not found sufficient to obviate the rejections under 35 U.S.C. §§ 102 and/or 103 as being anticipated by Fleming et al. (1999), or obvious over Fleming et al. (1999) in view of cited secondary references. Fleming et al. is prior art under §102(b); and where a rejection constitutes a statutory bar, such a declaration cannot be relied upon to obviate that rejection.

Priority

9. Although this application claims under 35 USC § 119(e) the earlier filing date of the U.S. Provisional Application Serial No. 60/204,284, filed May 15, 2000, claims 12-50, 52, 53, 55, 56, 58, 59, 61-73, and 75-78 do not properly benefit under 35 U.S.C. § 119(e) by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

At page 17 of the amendment filed September 1, 2006, Applicant has disagreed, asserting that, as currently amended, the claims are entitled to the claimed benefit.

Applicant's remarks have been carefully considered but are not persuasive, as the rejections of the claims under § 112, first paragraph, have been maintained for the reasons set forth below.

Grounds of Objection and Rejection Withdrawn

10. Unless specifically reiterated below, the amendment or arguments filed September 1, 2006, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed March 2, 2006.

Grounds of Objection and Rejection Maintained

Claim Rejections - 35 USC § 112

11. The rejection of claims 12-50, 52, 53, 55, 56, 58, 59, 61-73, and 75-78 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is maintained.

This is a "written description" rejection.

Beginning at page 24 of the amendment filed September 1, 2006, Applicant has traversed the grounds of rejection set forth in section 15, beginning at page 32, of the preceding Office action.

Applicant has argued, because monoclonal antibodies 4D5 and 520C9 are known to be inhibit the growth of cancer cells or shown to induce antibody dependent apoptosis of human breast cancer cells, and because the present claims are directed to antibodies that bind to the same epitope as the epitope to which monoclonal antibodies 4D5 or 520C9 bind, the written description requirement set forth under 35 U.S.C. §112, fist paragraph, has been met.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Referring to page 35 of the preceding Office action mailed March 2, 2006, Applicant has remarked that the Examiner has acknowledged that ant-HER2 antibodies with the specificity of the 4D5 antibody have been found to be effective in inhibiting growth of cancer cells.

To the contrary, the preceding Office action, at page 35, states:

> [A]part from Herceptin™, it appears the specification fails to describe an antibody that is *not* conjugated to a toxin moiety (e.g., a radionuclide or chemotherapeutic agent), which inhibits the growth of cancer cells *in vivo*. Inasmuch as the clinical effectiveness of Herceptin™ (i.e., a naked recombinant humanized version of murine monoclonal antibody 4D5) appears *unique*, it is noteworthy that the specification fails to describe the genus of antibodies to which the claims are directed as binding specifically to the same "epitope" of HER2 as monoclonal antibody 4D5 and Herceptin™. Moreover, the specification does not describe the one, or possibly more "epitopes" to which the genus

of antibodies must bind, if not conjugated to a cytotoxic moiety, so as to yield the claimed therapeutic effect *in vivo* during the practice of the claimed invention.

Additionally, as explained at page 34 of the preceding Office action, only the *recombinant humanized* version of the murine antibody (i.e., Herceptin™ (Trastuzumab)) has been shown to mediate ADCC; murine monoclonal antibody 4D5 does not. Accordingly, in response to Applicant's argument, it is not by mere virtue of the epitope to which an antibody binds that the antibody has such activity.

Furthermore, as explained in the Office action mailed February 18, 2005, Lewis et al. (of record) teaches murine monoclonal antibody 4D5 does not affect the proliferation of gastric and colon cancer cells, even though these cells express an amount of HER2 that is equivalent to the amount expressed by breast cancer cells that are sensitive to the effects of treatment with the antibody. Therefore, again, it is not by mere virtue of the epitope to which an antibody binds that the antibody has anti-proliferative effects upon cancer cells expressing HER2.

Applicant has remarked, as evidenced by Stockmeyer et al. (2003), monoclonal antibody 520C9 is capable of mediating ADCC of human breast cancer cells in the presence of polymorphonuclear granulocytes. Responding to these remarks, as explained in the preceding Office actions, even though the prior art teaches monoclonal antibody 520C9 is capable of mediating ADCC, its ability to do so appears relatively unique and its use *in vivo* to achieve therapeutic benefit in treating cancer overexpressing HER2 has apparently not been reported; see, e.g., pages 14 and 15 of the preceding Office action mailed February 18, 2005. Stockmeyer et al. (2003) discusses the results of *in vitro* studies, which were designed to further characterize the mechanism by which polymorphonuclear granulocytes induce cell death, but does not establish the clinical or therapeutic effectiveness of monoclonal antibody 520C9. Again, while the art teaches that an immunotoxin comprising this antibody can be used to inhibit the growth of tumor cells, there appear no reports that the monoclonal antibody itself, or any fragment thereof, is capable of effectively inhibiting the growth of tumor cells *in vivo*. Notably, Keler et al. (of record) demonstrates the $F(ab')_2$ fragment of monoclonal antibody 520C9 is relatively incapable of mediating ADCC compared to

MDX-H210, a recombinant bispecific antibody comprising a Fab' fragment of 520C9. Again, it is not by mere virtue of the epitope to which an antibody binds that the antibody has anti-proliferative effects upon cancer cells expressing HER2.

Moreover, regardless of the specific epitope to which the anti-HER2 antibody binds, as further explained in the preceding Office actions, few *naked* antibodies have been described which are capable of achieving clinically or therapeutically significant benefits in treating cancer. As mentioned above, Herceptin™ seems the notable exception, inasmuch as it has been shown clinically effective, alone and/or in combination with other anticancer drugs, to inhibit the growth of breast cancer characterized by the overexpression of HER2.

As a new matter necessitated by the amendment, claims 12, 16, and 42 are directed to a genus of antibodies having "anti-tumor activity", as well as a genus of biologically active variants of an IL-2 molecule comprising the amino acid sequence of SEQ ID NO: 1, which have "anti-tumor" activity.

At page 4, lines 11-22, the specification discloses the following:

> By "anti-tumor activity" is intended a reduction in the rate of cell proliferation, and hence a decline in growth rate of an existing tumor or in a tumor that arises during therapy, and/or destruction of existing neoplastic (tumor) cells or newly formed neoplastic cells, and hence a decrease in the overall size of a tumor during therapy.

The antibodies to which the claims are directed necessarily bind the epitope recognized by either of monoclonal antibodies 4D5 or 520C9, but are nonetheless structurally unrelated.

The biologically active variants of the IL-2 molecule to which the claims are directed must comprise an amino acid sequence having at least 90% identity to SEQ ID NO: 1, as calculated in accordance with the claims, but nonetheless vary in their structures.

Notably, the members of the genus of antibodies to which the claims are directed and the members of the genus of biologically active variants of an IL-2 molecule comprising the amino acid sequence of SEQ ID NO: 1 are not structurally related; yet, according to the claims, they possess the same anti-tumor activity.

These facts illustrate a lack of correlation between any one particularly identifying (i.e., substantial) structural feature and any one particularly identifying functional feature, which, if otherwise disclosed, would permit the skilled artisan to immediately envision, recognize or distinguish the antibodies and the biologically active variants of the IL-2 molecule comprising SEQ ID NO: 1 to which the claims are directed.

Again, "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that adequately describes the genus of anti-HER2 antibodies having anti-tumor activity, which when *not* conjugated to a cytotoxic moiety, inhibit the growth of cancer cells, so as to achieve the claimed effect. Similarly, there is no language that adequately describes the genus of biologically active variants of an IL-2 molecule comprising amino acid sequence of SEQ ID NO: 1 having anti-tumor activity, which when administered in combination with the antibody inhibits the growth of cancer cells, so as to achieve the claimed effect. *A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.*

Again, the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997).

As further explained in the preceding Office action, although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1984 (CAFC 2004). Without the antibody and the biologically active variant of an IL-2 molecule comprising the amino acid sequence of SEQ ID NO: 1, it is impossible to use the claimed invention.

Although the skilled artisan could potentially screen candidate anti-HER2 antibodies and variants of the IL-2 molecule comprising SEQ ID NO: 1 to identify those that might be used in practicing the claimed invention to achieve the claimed effect, again, the written description provision of 35 U.S.C. § 112 is severable from its enablement provision. See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991); *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

As an additional matter necessitated by the amendment, claims 12, 16, 17, and 42 are directed to a genus of antibodies having anti-tumor activity, which bind to the same epitope as an antibody selected from the group consisting of 4D5 and 520C9. However, as noted above, the epitope to which the antibody binds does not suffice to determine the effectiveness of the antibody to inhibit the growth of cancer cells; consequently, there is no correlation between the ability of an antibody to bind to either one of the epitopes recognized by monoclonal antibodies 4D5 or 520C9 and its ability to act effectively as an inhibitor of the growth or proliferation of breast cancer cells. Therefore, even if one were capable of recognizing or distinguishing antibodies that bind to one or the other epitope of HER2, it would still not be possible to immediately envision, recognize, or distinguish those suitable for use in practicing the claimed invention to achieve the claimed therapeutic effect.

Furthermore, despite any presumption otherwise, the instant disclosure would not provide a written description of the claimed invention, which would suffice to permit the skilled artisan to immediately envision, recognize or distinguish antibodies that bind the same epitope of HER2 recognized by either monoclonal antibody 4D5 or 520C9.

The term "epitope", as it is used in the art of immunology, is more generally used in a broader context to mean an "antigenic determinant", or site on the surface of an antigen molecule to which a single immunoglobulin molecule (e.g., antibody), Major Histocompatibility Complex (MHC) antigen, B-cell receptor, or T-cell receptor binds; generally an antigen has several or many different antigenic determinants and reacts with antibodies, MHC antigens, B-cell receptors, and T-cell receptors of many different

specificities. Stedman's Online Medical Dictionary, 27th Edition, which is available on the Internet at http://www.stedmans.com/, for example, defines the term "epitope' as "[t]he simplest form of an antigenic determinant, on a complex antigenic molecule, which can combine with antibody or T cell receptor".

Greenspan et al. (*Nature Biotechnology.* 1999; **7**: 936-937), for example, teaches that defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include any and all residues that make contact with a ligand (e.g., an antibody), even contacts by residues that are energetically neutral, or even destablilizing to binding are constitutive. Greenspan et al. teaches an epitope will not include any residue not contacted by the ligand (e.g., an antibody), even though substitution of such a residue by another might profoundly affect binding. Accordingly, it follows the epitope to which any given ligand (e.g., an antibody) binds can only be identified empirically; moreover, it is only possible to determine if an antibody binds to the same epitope as another antibody by determining to which epitope(s) each of the antibodies binds, so as to empirically establish their identity or lack thereof.

Even using a competition binding assay, the skilled artisan cannot recognize or distinguish a ligand, e.g., an antibody that binds the same epitope as another ligand because ligands that compete with one another for binding to the same antigen do not necessarily bind the same epitope; rather, a ligand may bind a spatially overlapping but distinct epitope and thereby sterically hinder binding of the other ligand to its epitope.

Notably, the specification does not teach the epitope of HER2, as defined by Greenspan et al., to which either monoclonal antibody 4D5 or 520C9 binds; so it follows that the skilled artisan could not immediately distinguish the antibodies to which the claims are directed, as it would be necessary to know the epitopes to which these antibodies bind and also determine the epitope to which any other anti-HER2 antibody binds to establish whether the latter binds to the same epitope as either of the former antibodies.

As observed in the preceding Office action, the Federal Circuit recently decided that the description of a fully characterized molecular target of an antibody is sufficient to adequately describe an antibody that binds that target. See *Noelle v. Lederman*, 69 USPQ2d 1508 (CA FC 2004). However, the same court decided that each case involving the issue of written description, "must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited." *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977)).

Following the example set by the Federal Circuit in deciding *Noelle v. Lederman*, *were* the claims directed to an antibody that binds a well-characterized antigen, the written description would be met. In this instance, however, the claims are not directed to an antibody that binds a well-characterized molecular target, but rather to an antibody that binds to the very discrete parts (i.e., epitopes) of HER2, which are recognized as antigenic determinants by monoclonal antibodies 4D5 and 520C9.

In addition, as explained above, there is factual evidence that the detailed description of an antigen, as opposed to the detailed description of an epitope of an antigen, should not always be regarded as sufficient to describe the antibody that binds that antigen, particularly in instances where binding of the antibody modulates the activity of the antigen or affects the growth of a cell expressing the antigen. For example, Stancoviski et al. (of record) characterized the binding effects of different anti-HER2 antibodies, which bind different epitopes of the antigen, upon the growth of tumor cells; see entire document (e.g., the abstract). Stancovski et al. teaches some anti-ErbB2 antibodies inhibited tumor cell growth, but others actually accelerated their growth (page 8693, column 1). Accordingly, the mere generalized description of antibodies that bind a well-characterized antigen, as opposed to a well-characterized epitope of an antigen, cannot always suffice to describe adequately antibodies that have, for example, an inhibitory or therapeutic effect, because the skilled artisan could not immediately envision, recognize, or distinguish those antibodies that bind an antigen on tumor cells and inhibit the growth of those tumor cells from antibodies that bind the antigen but lack therapeutic effect (e.g., promote the growth of tumor cells). In this instance, the claims are directed to antibodies that are useful in inhibiting the growth of

tumor cells expressing HER2, which are suitable for use in practicing the claimed invention to achieve the claimed therapeutic effect.

For clarity, claims 74 and 79 have not been rejected as lacking sufficient written description, because claim 74 is directed to the method of claim 12 for treating breast cancer characterized by the overexpression of HER2, wherein said anti-HER2 antibody is Herceptin™ and said IL-2 polypeptide comprises the amino acid sequence of SEQ ID NO: 1 or is des-alanyl-1, serine-125 human interleukin-2 (i.e., aldesleukin), whereas claim 79 is directed to the method of claim 63 for treating breast cancer characterized by the overexpression of HER2, wherein said anti-HER2 antibody is Herceptin™.

12. The rejection of claims 12-50, 52, 53, 55, 56, 58, 59, 61-73, and 75-78 under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for** using a method for treating a patient diagnosed with breast cancer that overexpresses HER2 comprising administering to the patient a therapeutically effective amount of Herceptin™ (trastuzumab) or an immunotoxin comprised of a humanized version of murine antibody 4D5, murine antibody 520C9, or another anti-HER2 antibody, as taught by the prior art, in combination with a therapeutically effective amount of naturally occurring human IL-2, Proleukin™ (aldesleukin), or another recombinant human "IL-2" molecule effective to stimulate non-specific immune response in humans, as taught by the prior art, **does not reasonably provide enablement for** using a method for treating a subject having breast cancer that is characterized by overexpression of HER2 according to the claims, is maintained. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Beginning at page 18 of the amendment filed September 1, 2006, Applicant has traversed the grounds of rejection set forth in section 10, beginning at page 12, of the preceding Office action.

Applicant has argued, contrary to the Office's position, that the disclosure would have been sufficient to have enabled the skilled artisan to practice the claimed invention

without undue and/or unreasonable experimentation in fulfillment of the enablement requirement set forth under 35 U.S.C. § 112, first paragraph.

Applicant's argument has been carefully considered but not found persuasive for the following reasons:

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

Contrary to Applicant's assertions careful consideration of these factors indicates the claimed invention could not be used without undue and/or unreasonable experimentation.

As explained in the preceding Office actions, the references cited in support of the Office's position (e.g., Stancovski et al; Lewis et al.) clearly indicate the skilled artisan cannot reliably and accurately predict which antibodies that binds the extracellular domain of HER2 ameliorate or aggravate disease symptoms in a subject

afflicted with cancer, since it is not possible to predict which of such antibodies will inhibit or enhance the growth of cancer cells, and which will have no effect. Moreover, the skilled artisan cannot predict whether any given antibody, even an antibody that binds to the same epitope as either of monoclonal antibody 4D5 or 520C9, can be used in practicing the claimed invention to achieve the claimed therapeutic effect. Reimer et al. (of record), for example, teaches the diverse biological effects of anti-HER2 antibodies depends upon their varying epitope specificities; but, as explained in the above "written description" rejection, it is not by mere virtue of the epitope to which an antibody binds that the antibody has anti-proliferative effects upon cancer cells expressing HER2. For example, while Herceptin™ is capable of inducing ADCC, the parental, murine monoclonal antibody, designated 4D5, lacks this capability; yet, as noted in the preceding Office action, it appears from Applicant's disclosure that any greater effectiveness of the exemplified combination, per se, of Herceptin™ (i.e., Trastuzumab, a recombinant humanized version of murine monoclonal antibody 4D5) and Proleukin™ (i.e., Aldesleukin, a recombinant human IL-2 mutein), as compared to that of the monotherapeutic use of the antibody, would depend upon the ability of the antibody to mediate antibody-dependent cell cytotoxicity (ADCC).

As further explained in the preceding Office action, the concept of treating cancer by coadministering IL-2 and an antitumor monoclonal antibody capable of inducing antibody-dependent cellular cytotoxicity is not novel; for example, as early as 1988 investigators, such as Kawase et al. (of record) were using such combined therapy to treat lymphokine-activated killer-resistant tumors in mice.

If the effectiveness of the exemplary combination of Herceptin™ and Proleukin™ is not dependent upon the ability of the antibody to mediate ADCC, then, the presence of IL-2-activated effector cells would not be expected to enhance the antiproliferative, i.e., therapeutic, effect of an anti-HER2 antibody.

However, the claims are not limited to any such proven combination, but are instead more broadly directed to a combination of any member of a genus of anti-HER2 antibodies that bind the same epitope of HER2 as either monoclonal antibody 4D5 or

5290C9 and an IL-2 molecule comprising the amino acid sequence of SEQ ID NO: 1 or any biologically active variant thereof comprising a similar amino acid sequence.

As has been explained, the recombinant humanized version of the murine monoclonal antibody 4D5, namely Herceptin™ has been shown to mediate ADCC; and the conventional wisdom in the art is that it is by this mechanism, albeit not by this mechanism alone, that Herceptin™ mediates its growth inhibitory effects upon tumors in patients. However, Lewis et al. (of record) teaches that the *murine* monoclonal antibody does not mediate ADCC, and is further incapable of fixing complement to mediate complement-mediated cell cytotoxicity. Thus, if by no other mechanism Herceptin™ achieves its effectiveness, the teachings of Lewis et al. suggest that because the murine antibody does not mediate ADCC, a murine anti-HER2 antibody that binds the extracellular domain of HER2, even one that binds to the same epitope as monoclonal antibody 4D5, cannot be used in practicing the claimed invention to achieve the claimed therapeutic effect before first determining whether the antibody effectively inhibits the growth of cancer cells in patients by some other mechanism and whether administering IL-2 in combination with the antibody will enhance or perturb this mechanism.

As has also been explained in the preceding Office action, Stancovski et al. (of record) teaches none of the disclosed anti-HER2 antibodies, which inhibited the growth of tumor cells, mediated ADCC. Thus, these teachings suggest the mechanism by which mouse anti-HER2 antibodies typically affect the proliferation of cells is not effector cell (e.g., NK cell)-dependent, and further suggests that monoclonal antibody 520C9, as a murine antibody, is unusual in its ability to mediate ADCC.

For these reasons, it is submitted that murine anti-HER2 antibodies, including mouse monoclonal antibody 4D5 or any other non-human antibody that binds the same epitope, should not generally be regarded as suitable for use in the practice of the claimed invention, since most murine antibodies lack the ability to mediate ADCC in humans and are therefore not therapeutically equivalent to Herceptin™.

Furthermore, even though monoclonal antibody 520C9 is capable of mediating ADCC, it use in practicing the claimed invention to achieve the claimed therapeutic

effect in patients afflicted with breast cancer has not been exemplified or otherwise demonstrated.

Again, while the art teaches that a bispecific recombinant antibody comprising an antigen-binding fragment of monoclonal antibody 520C9 and an immunotoxin comprising the antibody are capable of inhibiting the growth of tumor cells, the prior art does not teach that monoclonal antibody 520C9 itself, or any fragment thereof, is capable of effectively inhibiting the growth of tumor cells *in vivo*. To the contrary, Keler et al. (of record) teaches the $F(ab')_2$ fragment of monoclonal antibody 520C9 is relatively incapable of mediating ADCC, as compared to MDX-H210, a recombinant bispecific antibody comprising a Fab' fragment of 520C9.

Furthermore, as explained previously, it has long been known that the ability of an antitumor antibody to induce ADCC and complement-mediated cell cytotoxicity is at least partially dependent upon the isotype of the antibody. For example, Masui et al. (of record) teaches anti-EGFR antibodies mediate antitumor effects by different mechanisms, which are at least partially determined by the different isotypes of these antibodies; and more recently, Kim et al. (of record) determined using anti-HER2 antibodies that both isotype *and epitope specificity* are important determinants of the antitumor effect of the antibodies.

More particularly, Kim et al. (of record) teaches none of the antibodies specific for one of two epitopes suppressed the growth of cancer cells *in vivo*, despite the fact that these antibodies had demonstrated considerable antitumor activity *in vitro*. In contrast, Kim et al. teaches each of the antibodies specific for the other epitope showed antitumor activities *in vivo*. Kim et al. discloses, "[i]t was surprising that HRT G2b [i.e., the antibody of IgG2b isotype] was most effective among the HRT isotype antibodies *in vivo*, whereas the HRT G2a [i.e., the antibody of IgG2a isotype] showed only a slight effect" (page 433, column 1). Kim et al. concludes the results of the *in vivo* studies could not be explained by the results obtained from the *in vitro* studies, which suggests the antitumor effects of these antibodies might involve still other mechanisms not yet identified or understood. Nevertheless, Kim et al. teaches their results clearly indicate that the epitope specificity of antitumor antibodies, in addition to their isotypes,

determines their ability to exert effective antitumor activity both *in vitro* and *in vivo* (page 433, column 1). Given the complexity and unpredictability made evident by the teachings of Kim et al., it is submitted that the skilled artisan could not practice of the claimed invention without undue and/or unreasonable experimentation.

As previously explained, it is not sufficient to merely know that an antibody binds the extracellular domain of HER2, or even to the same epitope of the antigen as another antibody, as it cannot be predicted whether the antibody will be effective to inhibit cancer cells. Moreover, in light of Kim et al., it is also not sufficient to merely know that an antibody that binds the extracellular domain of HER2 is capable of mediating ADCC or CDC *in vitro*, as it cannot be predicted whether the antibody will be effective *in vivo*. Kim et al. also underscores the conclusions that have been made on the basis of the teachings of Stancovski et al. and Lewis et al.; Kim et al. also teaches the epitope specificity is an important determinant of the antitumor activity of an anti-HER2 antibody.

Further demonstrating this complexity, as well as the unpredictability in this area of the art, Vuist et al. (of record) teaches treatment of cancer cells with an antitumor antibody of the isotype IgG2a was therapeutically active by itself; however, Vuist et al. teaches IgG1 and IgG2b isotype variants of this antitumor antibody were not active alone to inhibit the growth of the cells. As noted in the preceding Office action, although both IgG1 and IgG2b isotype variants were ineffective alone, Vuist et al. teaches their combination with recombinant IL-2 resulted in significant antitumor effects. The antibody of IgG2a isotype, which was effective alone, was more so in combination with recombinant IL-2. Vuist et al. discloses further characterization of these antibodies using *in vitro* studies suggests the isotypes that were ineffective alone (i.e., IgG1 and IgG2b) mediated IL-2-induced ADCC activity of lymphocytes in the presence of IL-2. Vuist et al. speculates that in the presence of IL-2 the antitumor activity of the antibody of IgG2a isotype may involve both IL-2-induced ADCC activity of lymphocytes and IgG2a-restricted antitumor activity of monocytes/macrophages. Thus, contrasting other disclosures, such as Kim et al. (*supra*), Vuist et al. provides factual evidence that mere knowledge of the isotype of an antitumor antibody does not provide a fair indication that

the antibody in combination with IL-2 will be capable of mediating ADCC *in vivo*, so as to be therapeutically effective and useful in the practice of the claimed invention. Furthermore, the teachings of Vuist et al. suggest mere identification of anti-HER2 antibodies capable of inhibiting the growth of cancer cells will not provide reliable indication that the antibody can or cannot be used in combination with IL-2 to treat cancer *in vivo*, since Vuist et al. discloses effective treatment of cancer cells with antibodies, which were not effective alone, in the presence of IL-2.

Additionally, regardless of the specific epitope to which the anti-HER2 antibody binds, few *naked* antibodies have been described which are capable of achieving clinically or therapeutically significant benefits in treating cancer. Again, Herceptin™ seems the notable exception, inasmuch as it has been shown clinically effective, alone and/or in combination with other anticancer drugs, to inhibit the growth of breast cancer characterized by the overexpression of HER2.

Yet, while the claims are directed to an antibody that binds to the same epitope as monoclonal antibody 4D5, the claims are not limited to humanized versions of the monoclonal antibody, such as Herceptin™, which are known or expected to have the capability of inducing ADCC in humans.

Furthermore, as also explained in the "written description" rejection and again above, even though the prior art teaches monoclonal antibody 520C9 is capable of mediating ADCC, its ability to do so appears relatively unique; and while the prior art teaches that an immunotoxin comprising this antibody can be used to inhibit the growth of tumor cells, there are no reports that the monoclonal antibody itself, or any fragment thereof, is capable of effectively inhibiting the growth of tumor cells *in vivo*. Once again, Keler et al. (of record) demonstrated the $F(ab')_2$ fragment of monoclonal antibody 520C9 is relatively incapable of mediating ADCC compared to MDX-H210, a recombinant bispecific antibody comprising a Fab' fragment of 520C9. Therefore, again, it should not be said an anti-HER2 antibody has anti-proliferative effects upon cancer cells expressing HER2 as a mere consequence of its epitope binding specificity.

Accordingly, the references indicate that merely knowing that a given antibody binds the extracellular domain of HER2, or even to any one particular epitope of the

antigen will not suffice to enable the skilled artisan to use the claimed invention to treat cancer in a subject without undue and/or unreasonable experimentation. Instead, it would first be necessary to determine *if* the antibody is effective to inhibit the growth of breast cancer cells characterized by the overexpression of HER2 *in vivo*.

While it may be a matter of routine to screen anti-HER2 antibodies that bind the extracellular domain of HER2 to identify those that are capable of inhibiting the growth of breast cancer cells characterized by the overexpression of HER2 *in vitro*, the claims are notably not drawn to such antibodies. Rather the claims are drawn to a method for treating such cancers in a subject by administering such antibodies in combination with IL-2 or a biologically active variant thereof.

The references cited in the preceding Office action establish the fact that given the level of knowledge and skill in the art the disclosure would not been reasonably enabling of the claimed invention, as the skilled artisan could not make and/or use the claimed invention without first performing the undue and/or unreasonable experimentation that would be necessary to determine *if* the claimed invention can be used to achieve the claimed therapeutic effect. For example, given the knowledge and skill in the art, while the specification reasonably enables the use of a method for treating a patient diagnosed with breast cancer that overexpresses HER2, said method comprising administering to the patient a therapeutically effective amount of Herceptin™ (Trastuzumab) in combination with a therapeutically effective amount of Proleukin™ (Aldesleukin), the claims are directed to methods for treating such cancer comprising administering any antibody that binds to the same epitope as either of the monoclonal antibodies 4D5 or 520C9 together with an IL-2 molecule comprising the amino acid sequence of SEQ ID NO: 1 or any biologically variant thereof comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 1.

M.P.E.P. § 2164.08 states, "the scope of enablement must only bear a 'reasonable correlation' to the scope of the claims" to satisfy the enablement provision set forth under 35 U.S.C. § 112, first paragraph. However, in this instance, given the

disparity in the scope of enablement and the scope of the claims, it is submitted the former does not bear "reasonable correlation" to the latter.

In this instance, the claims are directed to a genus of antibodies, which bind to one or the other epitope recognized by monoclonal antibody 4D5 or 520C9. However, the epitopes to which these antibodies bind have not been described; so, for reasons explained in the "written description" rejection, the skilled artisan could not "make" (e.g., select) the antibody to which the claims are directed without undue and/or unreasonable experimentation. As taught by Greene et al. (*supra*), the epitope to which any given antibody binds must be empirically determined; so, to determine whether any one antibody binds the same epitope as another antibody would require separate determinations of both epitopes. Only after such determinations were made would it then be possible to distinguish an antibody that binds HER2 binds by recognizing the same epitope as one of the epitopes recognized by monoclonal antibody 4D5 and 520C9.

As an additional matter, whereas the previous claims were directed to a genus of variants of an IL-2 molecule, which activate NK cells, the present claims are directed to a different genus of molecules comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 1, which have "anti-tumor activity. As would be understood given the above mentioned definition of the term "anti-tumor activity", these biologically active variants of IL-2 are necessarily capable of causing a reduction in the rate of cell proliferation, and hence a decline in growth rate of an existing tumor or in a tumor that arises during therapy, and/or causing the destruction of existing neoplastic (tumor) cells or newly formed neoplastic cells, and hence a decrease in the overall size of a tumor during therapy. Accordingly, if by no other means, the biologically active variants of the IL-2 molecule comprising SEQ ID NO: 1 to which the claims are directed would have to be made and then selected upon the basis of very complicated *in vivo* experiments designed to determine whether the molecules could be used effectively to cause a reduction in tumor growth and/or tumor burden. Inasmuch, as this is the very intent for which the claimed invention is to be practiced, it is submitted the claimed invention cannot be used without undue and unreasonable experimentation, as it would require

the practitioner to first elaborate a means for practicing the invention to achieve the claimed therapeutic effect.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), there appears a preponderance of factual evidence of record indicating the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

For clarity, claims 74 and 79 have not been rejected as lacking a reasonably enabling disclosure, because claim 74 is directed to the method of claim 12 for treating breast cancer characterized by the overexpression of HER2, wherein said anti-HER2 antibody is Herceptin™ (trastuzumab) and said IL-2 polypeptide comprises the amino acid sequence of SEQ ID NO: 1 or is des-alanyl-1, serine-125 human interleukin-2 (i.e., aldesleukin), whereas claim 79 is directed to the method of claim 63 for treating breast cancer characterized by the overexpression of HER2, wherein said anti-HER2 antibody is Herceptin™.

13. The rejection of claims 12-50, 52, 53, 55, 56, 58, 59, and 61-73 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Beginning at page 20 of the amendment filed September 1, 2006, Applicant has traversed the grounds of rejection set forth in section 11, beginning at page 22, of the preceding Office action.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued antibodies 4D5 and 520C9 are known and readily available, inasmuch as both antibodies are commercially available to the public without restriction from the ATCC.

In response the ATCC catalog indicates that hybridoma cell lines designated "A-HER2 [4D5; NB9644P28]" and "520C9 [520C9.C3B10T]" bearing ATCC accession numbers CRL-10463™ and HB-8696™, respectively, are commercially available with the provision that the terms and conditions of ATCC's Material Transfer Agreement or, in certain cases, an MTA specified by the depositing institution be read and accepted. In addition, the catalog indicates that the materials are cited in a U.S. and/or other Patent or Patent Applications, and may not be used to infringe on the patent claims.

Applicant has not made of record any of the facts and circumstances surrounding the access to the biological materials from said depository, which are dictated by the terms and conditions of ATCC's Material Transfer Agreement or, in certain cases, an MTA specified by the depositing institution.

Notably, too, the ATCC catalog indicates, "ATCC products are intended fro laboratory research purposes only", and "are not intended for use in humans"; see, e.g., page 2 of 3 of the copy of the product description for ATCC Number CRL-10463, which has been provided by Applicant as an attachment to the amendment filed September 1, 2006.

Because the claims encompass methods comprising administering these particular antibodies, it is particularly relevant to noted that these products, if acquired from the ATCC, cannot be used to practice the claimed invention in humans.

Additionally, as explained in the preceding Office action, Applicant has not established a nexus between these deposited materials and the antibodies to which the claims specifically refer.

Again, as explained in the preceding Office action, if Applicant can establish that hybridomas producing monoclonal antibodies 4D5 and 520C9 are known and readily available, the Office will accept the showing. However, establishing that these antibodies to which the claims refer are both known and readily available requires Applicant to provide a showing that antibodies, which are known and readily available,

are, in fact, the *same* antibodies to which the claims are directed. Such a showing provides a nexus "tying" together the antibodies to which the claims are directed and the antibodies allegedly known and readily available. Until such a nexus is identified in the specification, including the claims, as originally filed, in the absence of evidence that the hybridoma producing monoclonal antibodies 4D5 and 520C9 are readily available to the public and that all restrictions imposed by the depositor, or by other investigators on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, the rejection is properly maintained.

Applicant has further argued Herceptin™ is commercially available from Genentech, Inc.; however, as none of the rejected claims are specifically directed to Herceptin™, the issue of the readiness of public access is not presently at issue.

Having not resolved this issue, Applicant is again advised that a suitable deposit would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph (see 37 C.F.R. 1.801-1.809), provided the specification, as originally filed, provides a nexus to hybridomas producing same antibodies to which the claims are directed. See M.P.E.P. § 2406.01.

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by Applicant or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or

her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth under 37 CFR §§ 1.801-1.809 have been met.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Claim Rejections - 35 USC § 102

14. The rejection of claims 12-15, 17, 22-26, 35-37, 52, 58, 63, 64, 66, 68, 73, 75, and 77 under 35 U.S.C. 102(b) as being anticipated by Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) (of record), as evidenced by Fleming et al. (*Clin. Cancer Res.* 2002 Dec; **8**: 3718-3727), is maintained.

At page 25 of the amendment filed September 1, 2006, Applicant has traversed the grounds of rejection set forth in section 16, beginning at page 38, of the preceding Office action.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Fleming et al. teaches administering to patients a recombinant anti-HER2 monoclonal antibody in combination with IL-2. Fleming et al. teaches the antibody, as a single agent, has already been demonstrated to be therapeutically effective in treating patients afflicted with breast cancer characterized by the overexpression of HER2, and IL-2 activates natural killer cells *in vivo*. Fleming et al. teaches IL-2 doses were fixed at 1.25 MIU/m2 and administered subcutaneously (SQ) on a daily basis with "intermediate-dose" pulses of 15 MIU/m^2/day for 3 days every two weeks. Fleming et al. teaches the antibody was administered intravenously (IV) every two weeks prior to "intermediate-dose pulses". Fleming et al. teaches escalation of the dose of the antibody, which included doses of 1, 2, and 4 mg/kg. Fleming et al. disclosed no toxicity related to the

antibody, but they found dose-limited toxicity associated with IL-2. Fleming et al. teaches reducing the dose of IL-2 to 1 MIU/m^2 daily with 12 MIU/m^2 pulses, which was well tolerated. Fleming et al. teaches complete response and partial responses in three patients treated with 4 mg/kg doses of the antibody, all of which were afflicted with breast cancer characterized by overexpression of HER2; no objective clinical response was observed in the two patients afflicted with other types of cancer (i.e., head and neck cancer, ovarian cancer). Fleming et al. teaches no objective clinical response was observed in any of the patients when the dose of the antibody was less than 4 mg/kg.

Fleming et al. does not expressly disclose that the recombinant anti-HER2 monoclonal antibody administered to the patients is a humanized form of murine antibody 4D5. Nonetheless, as evidenced by Fleming et al. (2002), the antibody administered in this phase I trial was Herceptin™, which the specification discloses is a humanized form of murine antibody 4D5 that binds the extracellular domain of HER2; see, e.g., page 3720, column 1. As a humanized antibody, Herceptin™ comprises at least one human constant region.

Fleming et al. does not expressly disclose the therapeutically effective dose of IL-2 is "administered as" a lyophilized pharmaceutical composition. Nonetheless, Applicant has pointed out that such a lyophilized formulation could be administered by pulmonary inhalation, or it could be reconstituted into a liquid formulation, which could then be administered by any of several different routes (e.g., intravenous injection); see paragraph spanning pages 19 and 20 of the amendment filed September 1, 2006. Therefore, because Fleming et al. (2002) teaches the IL-2 was supplied as a lyophilized cake in vials and was reconstituted in sterile water for injection (see, e.g., page 3720, column 1), absent a showing of any difference, it is submitted the limitations of the claims have been met by the prior art.

Applicant has submitted a declaration under 37 C.F.R. § 1.132 by Michael Caligiuri, Neal Meropol, and Robert Schlisky, which is aimed to establish that Fleming et al. (1999) is not prior art under 35 U.S.C. § 102(a), as it is not a publication by "others". In response, the instant rejection has been made under § 102(b), constituting a statutory bar. As explained in the above discussion of the issue of priority, because

claims 12-50, 52, 53, 55, 56, 58, 59, 61-73, and 75-78 are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure, the effective filing date of the claims that are rejected is May 14, 2001. Accordingly, Fleming et al. (1999) is prior art under § 102(b). Where a rejection constitutes a statutory bar, a declaration, such as the declaration submitted by Applicant, cannot be relied upon to obviate that rejection. Accordingly, the merit of the declaration, as well as that of Applicant's argument, are presently moot.

Claim Rejections - 35 USC § 103

15. The rejection of claims 27-31, 53, and 59 under 35 U.S.C. 103(a) as being unpatentable over Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) (of record), as evidenced by Fleming et al. (*Clin. Cancer Res.* 2002 Dec; **8**: 3718-3727), in view of Meropol et al. (*Cancer Immunol. Immunother.* 1998; **46**: 318-326), is maintained.

At page 26 of the amendment filed September 1, 2006, Applicant has traversed the grounds of rejection set forth in section 17, beginning at page 39, of the preceding Office action.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Fleming et al. teaches that which is set forth in the above rejection of claims 12-15, 17, 22-26, 35-37, 52, 58, 63, 64, 66, 68, 73, 75, and 77 under 35 U.S.C. §102(b).

Fleming et al. does not expressly teach administering "recombinant" IL-2.

Nevertheless, Meropol et al. teaches aldesleukin, or Proleukin™; see entire document (e.g., page 319, column 1). Meropol et al. teaches such "recombinant" IL-2 is well tolerated and effective to stimulate expansion of natural killer cells over a prolonged course of treatment. Meropol et al. teaches as a next step in developing their program, they are undertaking a study combining daily subcutaneous administered low-dose IL-2, intermediate-dose pulses, and a humanized anti-HER2 monoclonal antibody in patients with cancers that overexpress HER2 (page 325, column 1).

Aldesleukin is "recombinant" IL-2, otherwise designated "des-alanyl-1, serine-125 human IL-2"; see, e.g., the specification, page 29, lines 1-11(as originally filed).

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have administered "recombinant" IL-2, or more particularly "des-alanyl-1, serine-125 human IL-2" (i.e., aldesleukin) together with Herceptin™ in practicing the process disclosed by Fleming et al. because Meropol et al. teaches such "recombinant" IL-2 is well-tolerated and effective to stimulate expansion of natural killer cells over a prolonged course of treatment, and moreover because Meropol et al. discloses studies using such a combination to treat patients afflicted with cancer characterized by overexpression of HER2 are already being undertaken. One ordinarily skilled in the art at the time the invention was made would have been motivated to do so to treat patients afflicted with breast cancer characterized by overexpression of HER2.

Applicant has submitted a declaration under 37 C.F.R. § 1.132 by Michael Caligiuri, Neal Meropol, and Robert Schlisky, which is aimed to establish that Fleming et al. (1999) is not prior art under 35 U.S.C. § 102(a), as it is not a publication by "others". However, as explained above, Fleming et al. (1999) is prior art under § 102(b); and where a rejection constitutes a statutory bar, a declaration, such as the declaration submitted by Applicant, cannot be relied upon to obviate that rejection. Accordingly, the merit of the declaration, as well as that of Applicant's argument, are presently moot.

16. The rejection of claims 27-31, 53, 59, and 65 under 35 U.S.C. 103(a) as being unpatentable over Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) (of record), as evidenced by Fleming et al. (*Clin. Cancer Res.* 2002 Dec; **8**: 3718-3727), in view of U.S. Patent No. 4,863,726 A (of record), is maintained.

Beginning at page 26 of the amendment filed September 1, 2006, Applicant has traversed the grounds of rejection set forth in section 18, beginning at page 40, of the preceding Office action.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Fleming et al. teaches that which is set forth in the above rejection of claims 12-15, 17, 22-26, 35-37, 52, 58, 63, 64, 66, 68, 73, 75, and 77 under 35 U.S.C. §102(b).

Fleming et al. does not expressly teach administering "recombinant" IL-2.

Nevertheless, U.S. Patent No. 4,863,726 A (Stevens et al.) teaches that which is set forth in the preceding Office actions[1]; see entire document. In particular, Stevens et al. teaches a "recombinant" IL-2, which is designated "des-ala$_1$-IL-2$_{ser}$125 mutein"; see, e.g., column 8, lines 46-55; column 24, lines 50-61. Furthermore, Stevens et al. teaches monoclonal antibody 520C9, which is used to make an immunotoxin effective in combination with recombinant IL-2 to treat mice bearing tumor cells to which the antibody binds; see, e.g., columns 23-25, Example II.

Absent a showing otherwise, the "recombinant" IL-2 disclosed by Stevens et al. is the "des-alanyl-1, serine-125 human IL-2" to which the claims refer.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have administered "recombinant" IL-2, or more particularly "des-alanyl-1, serine-125 human IL-2" (i.e., "des-ala$_1$-IL-2$_{ser}$125 mutein") in practicing the process disclosed by Fleming et al. because Stevens et al. teaches such "recombinant" IL-2, when used in combination with antitumor monoclonal antibodies to treat patients afflicted with tumors to which the antibodies bind, is effective to cause tumor reduction and/or augment LAK activity and moreover it was well appreciated in the art at the time the invention was made that "recombinant" IL-2 is, for example, more cost-effectively prepared than non-recombinant IL-2. In addition, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have administered "recombinant" IL-2, or more particularly "des-alanyl-1, serine-125 human IL-2" (i.e., "des-ala$_1$-IL-2$_{ser}$125 mutein") in combination with an effective amount of an immunotoxin comprised of a humanized form of monoclonal antibody 520C9, as opposed to Herceptin™, because using an animal model Stevens et al. teaches the

combination of such "recombinant" IL-2 and an immunotoxin comprised of the murine monoclonal antibody 520C9 is effective to treat tumors to which the antibody binds, and because Fleming et al. teaches administering humanized antibodies, as opposed to murine antibodies to patients, as it was well appreciated by one ordinarily skilled in the art at the time the invention was made that humanized antibodies are used preferentially in treating patients because they are less immunogenic than murine antibodies and can therefore be administered more safely to humans without the risk associated with administering murine antibodies. One ordinarily skilled in the art at the time the invention was made would have been motivated to do so to treat patients afflicted with breast tumors to which the immunotoxin comprised of the humanized.

Applicant has submitted a declaration under 37 C.F.R. § 1.132 by Michael Caligiuri, Neal Meropol, and Robert Schlisky, which is aimed to establish that Fleming et al. (1999) is not prior art under 35 U.S.C. § 102(a), as it is not a publication by "others". However, as explained above, Fleming et al. (1999) is prior art under § 102(b); and where a rejection constitutes a statutory bar, a declaration, such as the declaration submitted by Applicant, cannot be relied upon to obviate that rejection. Accordingly, the merit of the declaration, as well as that of Applicant's argument, are presently moot.

17. The rejection of claims 16, 32-34, 55, 56, and 67 under 35 U.S.C. 103(a) as being unpatentable over Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) (of record), as evidenced by Fleming et al. (*Clin. Cancer Res.* 2002 Dec; **8**: 3718-3727), in view of U.S. Patent Application Publication No. 2003/0185796 A1, is maintained.

At page 27 of the amendment filed September 1, 2006, Applicant has traversed the grounds of rejection set forth in section 19, beginning at page 42, of the preceding Office action.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

---

[1] See, e.g., the Office action mailed March 14, 2003, section 20, beginning at page 16; and the Office

Fleming et al. teaches that which is set forth in the above rejection of claims 12-15, 17, 22-26, 35-37, 52, 58, 63, 64, 66, 68, 73, 75, and 77 under 35 U.S.C. §102(b).

In particular, Fleming et al. teaches administering Herceptin™ every two weeks prior to "intermediate-dose" pulses of IL-2, which are administered for 3 days every two weeks to activate effector cells.

Fleming et al., however, does not expressly teach administering the antibody within 6 days of the initiation of a treatment period, as recited in claims 16 and 67.

U.S. Patent Application Publication No. 2003/0185796 A1 (Wolin et al.) teaches administering an anticancer monoclonal antibody in combination with IL-2; see entire document (e.g., the abstract). Wolin et al. teaches the dosing and scheduling can vary, so long as the treatment regimen provides beneficial therapeutic effects; see, e.g., paragraph [0017]; and paragraphs [0026]-[0062]. For example, Wolin et al. teaches multiple treatment cycles of variable duration to maintain NK cell count above an acceptable threshold level, wherein the duration of IL-2 administration is a function of the IL-2 dosing regimen used; see, e.g., paragraphs [0017], [0035], [0039], and [0116]. Wolin et al. teaches initial and subsequent treatment cycles are not necessarily the same; see, e.g., paragraph [0054]. Wolin et al. teaches both IL-2 and the antibody are administered concurrently on the same day, either at the same time (i.e., simultaneous administration) or at different times (i.e., sequential administration, in either order), or sequentially on different days; see, e.g., paragraph [0033]. At paragraph [0032], Wolin et al. teaches:

> [T]he two-level IL-2 dosing regimen is initiated prior to initiating weekly administration of therapeutically effective doses of anti-CD20 antibody. In this manner, a first dose of IL-2 is administered up to one month before the first dose of anti-CD20 antibody is administered. By "up to one month" is intended the first dose of IL-2 is administered at least one day before initiating anti-CD20 antibody administration, but not more than one month (i.e., 30 days) before initiating anti-CD20 antibody administration. Thus, IL-2 administration can begin, for example, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days (i.e., 1 week), 10 days, 14 days (i.e., two weeks), 17 days, 21 days (i.e., 3 weeks), 24 days, 28 days (4 weeks), or up to one month (i.e., 30 days) before administering the first therapeutically effective dose of the anti-CD20 antibody.

---

action mailed February 18, 2005, section 14, beginning at page 19, and section 15, beginning at page 22.

At paragraph [0018], Wolin et al. teaches, "[a]dministering of these two agents together in the manner set forth herein provides for greater therapeutic effectiveness than can be achieved using either of these agents alone, resulting in a positive therapeutic response that is improved with respect to that observed with either agent alone" and "the beneficial therapeutic effects of these agents can be achieved using lower cumulative dosages of IL-2, thereby lessening the toxicity of prolonged IL-2 administration and the potential for tumor escape". Wolin et al. teaches recombinant IL-2 is administered (e.g., Proleukin™); see, e.g., paragraphs [0056]-[0059]. In addition, Wolin et al. teaches different preparations of IL-2 may be formulated for use, including, for example, stabilized monomeric preparations and spray-dried preparations; see, e.g., paragraphs [0096]-[0100].

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have administered Herceptin™ to the patient following the initiation of a treatment period on any day preceding the administration of the first "intermediate-dose" pulse, since Wolin et al. teaches combining a two-level IL-2 dosing regimen and an anticancer antibody dosing regimen in which the IL-2 dosing regimen begins at, for example, 1 day, 2 days, 3 days, 4 days, 5 days, or 6 days before administering the first dose of the antibody. One ordinarily skilled in the art would have been motivated at the time the invention was made to practice the process disclosed by Fleming et al. by administering the antibody within, for example, 6 days of administering the first dose of IL-2 to the patient, so as to determine which schedule provides maximum therapeutic effect and/or optimal efficacy.

Applicant has submitted a declaration under 37 C.F.R. § 1.132 by Michael Caligiuri, Neal Meropol, and Robert Schlisky, which is aimed to establish that Fleming et al. (1999) is not prior art under 35 U.S.C. § 102(a), as it is not a publication by "others". However, as explained above, Fleming et al. (1999) is prior art under § 102(b); and where a rejection constitutes a statutory bar, a declaration, such as the declaration submitted by Applicant, cannot be relied upon to obviate that rejection. Accordingly, the merit of the declaration, as well as that of Applicant's argument, are presently moot.

18. The rejection of claims 18, 19, 38-40, 42-47, 61, 62, 69, and 70 under 35 U.S.C. 103(a) as being unpatentable over Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) (of record), as evidenced by Fleming et al. (*Clin. Cancer Res.* 2002 Dec; **8**: 3718-3727), in view of U.S. Patent Application Publication No. 2003/0185796 A1, as applied to claims 16, 32-34, 54, 55, and 67 above, and further in view of Sosman et al. (*J. Clin. Oncol.* 1993 Aug; **11** (8): 1496-1505), is maintained.

Beginning at page 27 of the amendment filed September 1, 2006, Applicant has traversed the grounds of rejection set forth in section 20, beginning at page 44, of the preceding Office action.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Fleming et al. teaches that which is set forth in the above rejection of claims 12-15, 17, 22-26, 35-37, 52, 58, 63, 64, 66, 68, 73, 75, and 77 under 35 U.S.C. §102(b).

U.S. Patent Application Publication No. 2003/0185796 A1 (Wolin et al.) teaches that which is set forth in the above rejection of claims 16, 32-34, 54, 55, and 67 are rejected under 35 U.S.C. 103(a).

However, none of the aforementioned references expressly teaches administering the antibody and IL-2 during an "introductory cycle", *per se*, which comprises daily administration of IL-2 through at least day 20 of the cycle and the administration of the antibody on day 7 of the cycle, as recited in claims 18, 42, and 69. Furthermore, none of the aforementioned references expressly teaches cycles of treatment that occur subsequently to such an "introductory cycle", which comprises administration of the antibody at day 1 and daily administration of IL-2 through at least day 14, as recited in claims 19, 47, and 70.

Sosman et al. teaches a phase I clinical trial combining monoclonal antibody therapy and IL-2 therapy in which patients were initially treated during a 20-day cycle; see entire document (e.g., the abstract).

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have administered Herceptin™ to the patient following

the initiation of an "introductory cycle" of treatment lasting at least 20 days, which comprises administering IL-2 daily and administering the antibody on day 7 of the cycle, preceding the administration of the first "intermediate-dose" pulse, since Wolin et al. teaches combining IL-2 therapy with antibody therapy during variable courses of an extended multicycle treatment regimens, which are adjusted so as to provide maximum therapeutic effect and/or optimal efficacy, and Sosman teaches an initial or "introductory" cycle of 20 days, which similarly comprises administering an antibody and IL-2. Furthermore, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have followed such an "introductory" treatment cycle with subsequent cycles of at least 14 days comprising administering the antibody on the first day of the cycle and administering IL-2 daily, since Wolin et al. teaches treatment regimens comprising multiple cycles, which are not necessarily the same, and may comprise administering the antibody on the first day of such a cycle and administering IL-2 on a daily basis for periods of, for example, two weeks. One ordinarily skilled in the art would have been motivated at the time the invention was made to practice the process disclosed by Fleming et al. by administering the antibody on day 7 of, for example, an initial treatment cycle of at least a 20 days comprising daily administrations of IL-2 to the patient, just preceding the administration of the first "intermediate-dose" pulse of IL-2, and then follow such an initial treatment cycle with subsequent treatment cycles comprising administering the antibody on the first day and administering IL-2 daily, so as to determine whether such a schedule provides maximum therapeutic effect and/or optimal efficacy.

Applicant has submitted a declaration under 37 C.F.R. § 1.132 by Michael Caligiuri, Neal Meropol, and Robert Schlisky, which is aimed to establish that Fleming et al. (1999) is not prior art under 35 U.S.C. § 102(a), as it is not a publication by "others". However, as explained above, Fleming et al. (1999) is prior art under § 102(b); and where a rejection constitutes a statutory bar, a declaration, such as the declaration submitted by Applicant, cannot be relied upon to obviate that rejection. Accordingly, the merit of the declaration, as well as that of Applicant's argument, are presently moot.

19. The rejection of claims 20, 21, 41, 48-50, 71, and 72 under 35 U.S.C. 103(a) as being unpatentable over Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) (of record), as evidenced by Fleming et al. (*Clin. Cancer Res.* 2002 Dec; **8**: 3718-3727), in view of U.S. Patent Application Publication No. 2003/0185796 A1 and Sosman et al. (*J. Clin. Oncol.* 1993 Aug; **11** (8): 1496-1505), as applied to claims 18 and 19 above, and further in view of Soiffer et al. (*Clin. Cancer Res.* 1996 Mar; **2** (3): 493-499), is maintained.

At page 28 of the amendment filed September 1, 2006, Applicant has traversed the grounds of rejection set forth in section 21, beginning at page 45, of the preceding Office action.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Fleming et al. teaches that which is set forth in the above rejection of claims 12-15, 17, 22-26, 35-37, 52, 58, 63, 64, 66, 68, 73, 75, and 77 under 35 U.S.C. §102(b). In particular, it is noted that Fleming et al. teaches a regimen comprising daily administration of low-dose IL-2 followed by "intermediate-dose" pulses for 3 days every two weeks.

U.S. Patent Application Publication No. 2003/0185796 A1 (Wolin et al.) teaches that which is set forth in the above rejection of claims16, 32-34, 54, 55, and 67 are rejected under 35 U.S.C. 103(a).

Sosman et al. teaches that which is set forth in the above rejection of claims 18 and 19 are rejected under 35 U.S.C. 103(a).

However, none of the aforementioned references expressly teaches weekly administration of "intermediate-dose" pulses of IL-2 during the "introductory cycle" of at least 20 days on days 8-10, or during subsequent cycles of at least 14 days on days 1-3, as recited in claims 20, 21, 41, 48-50, 71, and/or 72.

Soiffer et al. teaches a regimen comprising an introductory "priming" cycle of daily administration of low-dose IL-2 followed by "intermediate-dose" pulses (i.e., boluses) for 5 days every week; see entire document (e.g., the abstract; and page 494, Figure 1).

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have administered Herceptin™ to the patient following the initiation of an "introductory cycle" of treatment lasting at least 20 days, which comprises administering IL-2 daily and administering the antibody on day 7 of the cycle, preceding the administration of the first of three daily "intermediate-dose" pulses of IL-2 beginning on day 8 of the cycle, since Fleming et al. teaches a regimen comprising daily administration of low-dose IL-2 followed by "intermediate-dose" pulses for 3 days every two weeks, whereas Soiffer et al. teaches a regimen comprising an introductory "priming" cycle of daily administration of low-dose IL-2 followed by "intermediate-dose" pulses (i.e., boluses) for 5 days every week. Furthermore, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have followed such an "introductory" treatment cycle with subsequent cycles of at least 14 days comprising administering the antibody on the first day of the cycle, administering "intermediate-dose" pulses of IL-2 on days 1-3 of the cycle, and then after administering "low-dose" IL-2 daily, since, again, Fleming et al. teaches a regimen comprising daily administration of low-dose IL-2 followed by "intermediate-dose" pulses for 3 days every two weeks, Soiffer et al. teaches a regimen comprising an introductory "priming" cycle of daily administration of low-dose IL-2 followed by "intermediate-dose" pulses (i.e., boluses) for 5 days every week, and Wolin et al. teaches treatment regimens comprising multiple cycles, which are not necessarily the same, and may comprise administering the antibody and IL-2 on the first day of such a cycle. One ordinarily skilled in the art would have been motivated at the time the invention was made to do so in order to determine whether such a schedule provides maximum therapeutic effect and/or optimal efficacy.

Applicant has submitted a declaration under 37 C.F.R. § 1.132 by Michael Caligiuri, Neal Meropol, and Robert Schlisky, which is aimed to establish that Fleming et al. (1999) is not prior art under 35 U.S.C. § 102(a), as it is not a publication by "others". However, as explained above, Fleming et al. (1999) is prior art under § 102(b); and where a rejection constitutes a statutory bar, a declaration, such as the declaration

submitted by Applicant, cannot be relied upon to obviate that rejection. Accordingly, the merit of the declaration, as well as that of Applicant's argument, are presently moot.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

20. Claims 74-79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 74-79 contain the trademark/trade name Herceptin™. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe the recombinant, humanized anti-HER2 antibody derived from the murine monoclonal antibody 4D5 and, accordingly, the identification/description is indefinite.

21. Claims 12-50, 52, 53, 55, 56, 58, 59, and 61-79 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "new matter" rejection.

(a) Claims 12, 16, 17, 42, and 63 recite, "an interleukin-2 (IL-2) polypeptide comprising SEQ ID NO: 1".

At page 22 of the amendment filed September 1, 2006, Applicant has asserted the amendment finds support in the specification, as presently amended.

As presently amended at page 29 in the paragraph beginning in line 2, the specification reads:

> The IL-2 formulation in this study is manufactured by Chrion Corporation of Emeryville, California, under the tradename Proleukin. The IL-2 in this formulation is a recombinantly produced human IL-2 mutein, called aldesleukin, which differs from the native human IL-2 sequence (SEQ ID NO:1) in having the initial alanine residue eliminated and the cysteine residue at position 125 replaced by serine (referred to as des-alanyl-1, serine-125 human interleukin-2). This IL-2 mutein is expressed from E. coli, and subsequently purified by diafiltration and cation exchange chromatography as described in U.S. Patent No. 4,931,543.

Thus, the introduction of SEQ ID NO: 1 at page 29 by the amendment defines the native human IL-2 sequence as the amino acid sequence set forth as SEQ ID NO: 1.

Thus, while the inclusion of SEQ ID NO: 1 in the claims finds support in the specification, *as amended September 1, 2006*, the original disclosure provides no apparent nexus between the amino acid sequence set forth as SEQ ID NO: 1 and the amino acid sequence of the native human IL-2 molecule, which might serve as a basis for the amendment to the specification. If, as explained above, the amendment to the specification finds no written support in the specification, including the claims, as originally filed, then amending the claims to recite "SEQ ID NO: 1" introduces new matter and thereby violates the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

Furthermore, claims 12, 16, 17, and 42 recite "an interleukin-2 (IL-2) polypeptide comprising the sequence of SEQ ID NO:1 or a biologically active variant thereof [...] wherein said variant of IL-2 has anti-tumor activity and comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 1".

At page 14, lines 11-14, the specification discloses, "biologically active variants of IL-2 will generally have at least 70%, preferably at least 80%, more preferably about 90% to 95% or more, and most preferably about 98% or more amino acid sequence

identity to the amino acid sequence *of the reference polypeptide molecule, which serves as the basis for comparison*" (italicized for added emphasis).

Thus, this disclosure describes biologically active variants of "IL-2", which generally have at least 90% amino acid sequence identity to the amino acid sequence of the reference polypeptide, which serves as the basis of comparison. The term "IL-2" is explicitly defined in the specification at page 12, lines 8 and 9, to mean: "A lymphokine that is produced by normal peripheral blood lymphocytes and is present in the body at low concentrations". At page 12, lines 9-14, the specification further describes "IL-2" as first described by Morgan et al. (1976) and originally called T cell growth factor because of its ability to induce proliferation of stimulated T lymphocytes, and is a protein with a reported molecular weight in the range of 13,000 to 17,000 (Gillis and Watson (1980)) and has an isoelectric point in the range of 6-8.5.

However, the particular disclosure at page 14 of the specification does not provide written support for variants of a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, per se, nor does it provide written support for variants of such a polypeptide comprising amino acid sequences that are at least 90% identical to amino acid sequence of that polypeptide (i.e., SEQ ID NO: 1). Moreover, it appears that the specification only provides written support for suitable biologically active variants of native and naturally occurring IL-2, including "fragments", analogues", and "muteins", as opposed to variant of an IL-2 molecule comprising the amino acid sequence of SEQ ID NO: 1; see, in particular, page 13, lines 6 and 7.

For each of the above reasons, it appears the specification, as filed, fails to provide the necessary written support for the language of the present claims; consequently, the amendment of the claims appears to have introduced new matter or concepts in violation of the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

This issue might be resolved if Applicant were to point to particular disclosures in the specification, including the claims, as originally filed, which are believed to provide written support for language of the present claims.

(b) Claims 12, 16, 17, and 42 have been amended to recite, "wherein said anti-HER2 antibody or fragment thereof binds the same epitope as an anti-HER2 antibody selected from the group consisting of 4D5 and 520C9".

At page 15 of the amendment filed September 1, 2006, Applicant has asserted written support for the language of the amended claims is found in the specification, as filed, at, e.g., page 4, lines 14-19; page 22, lines 11-16; and page 24, lines 3 and 4.

The disclosure at page 4, lines 14-19, reads:

> By "anti-tumor activity" is intended a reduction in the rate of cell proliferation, and hence a decline in growth rate of an existing tumor or in a tumor that arises during therapy, and/or destruction of existing neoplastic (tumor) cells or newly formed neoplastic cells, and hence a decrease in the overall size of a tumor during therapy.

The disclosure at page 22, lines 11-16, reads:

> Anti-HER2 antibodies of murine origin and their humanized and chimeric versions are suitable for use in the methods of the present invention. Examples of such anti-HER2 antibodies include, but are not limited to, the 4D5 antibody (described in U.S. Pat. Nos. 5,677,171 and 5,772,997); and the 520C9 antibody and its functional equivalents, designated 452F2, 736G9, 741F8, 758G5, and 761B10 (described in U.S. Pat. No. 6,054,561); herein incorporated by reference.

The disclosure at page 24, lines 3 and 4, reads:

> Fragments of the anti-HER2 antibodies are suitable for use in the methods of the invention so long as they retain the desired affinity of the full-length antibody. Thus, a fragment of an anti-HER2 antibody will retain the ability to bind to the CD20 B-cell surface antigen.

None of these disclosures appear to describe a genus of anti-HER2 antibodies that bind the same epitope as either of murine anti-HER2 antibodies to which the claims are directed.

Elsewhere in the specification, there are disclosures pertaining to the epitope binding specificity of monoclonal antibodies. For example, at page 21, line 29, through page 22, line 2, the specification discloses:

> Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen.

Then, at page 28, lines 9-11, the specification describes a humanized anti-HER2 monoclonal (i.e., Herceptin™), which has recently has become available for clinical use, which recognizes an epitope overexpressed by at least 20% of a variety of tumor types, including breast, ovarian, gastric, non-small cell lung, and bladder.

However, none of these additional disclosures describe a genus of anti-HER2 antibodies that bind the same epitope as either of murine anti-HER2 antibodies to which the claims are directed.

The specification teaches a genus of antibodies that bind HER-2 (see, e.g., page 21, lines 23-25), albeit not necessarily antibodies that bind to any one particularly described epitope of the antigen; furthermore, the specification teaches particular examples of monoclonal antibodies (e.g., 4D5, and 520C9), which bind to different epitopes of the antigen.

However, Applicant is reminded that it cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See *In re Smith*, 173 USPQ 679, 683 (CCPA 1972). The specification fails to disclose the subgenus of antibodies that binds to the epitopes of HER2 to which the monoclonal antibodies 4D5 and 520C9 bind, which excludes other antibodies that bind different epitopes of HER2 not recognized by either one of these particular antibodies.

Adding the expressed exclusion of certain elements implies permissible inclusion of all other elements not so expressly excluded. This clearly illustrates that such negative limitations, in fact, introduce new concepts. See *Ex parte Grasselli*, 231 USPQ 393 (BPAI 1983).

MPEP § 2173.05(i) states on the basis of various case law, including *In re Johnson:* "Any negative limitation or exclusionary proviso must have basis in the original disclosure." In deciding *In re Johnson*, the Court decided that since appellant had described the genus *and* the species, which appellant had deliberately excluded from the claimed subject matter by the proviso exclusion of those species, appellant had not created "an artificial genus" (or an inadequately described subgenus), because the specification, having described the whole, must necessarily have described the part remaining after the proviso exclusion of the species. In this instance, however,

Applicant's disclosure does not include a description of the species Applicant wishes to exclude, nor does it include a description of the members of the genus they wish to include. In deciding *Ex parte Grasselli* (*Id.*), the Court decided that such an attempt to exclude species of a genus, which had not been described, introduces new matter into the specification as originally filed. See also *In re Welstead*, 59 CCPA 1105, 463 F.2d 1110, 174 USPQ 449 (1972); and *In re Lukach*, 58 CCPA 1233, 442 F.2d 967, 169 USPQ 795 (1971).

This issue might be remedied if Applicant were to point to any other particular disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support for the language of the instant claims; however, as noted at page 35 of the preceding Office action, the specification fails to describe a genus of antibodies as binding specifically to the same "epitope" of HER2 as monoclonal antibody 4D5 and Herceptin™, and moreover it does not describe the one, or possibly more "epitopes" to which the genus of antibodies must bind, if not conjugated to a cytotoxic moiety, so as to yield the claimed therapeutic effect *in vivo* during the practice of the claimed invention.

Accordingly, it appears the amendment to claims 12, 16, 17, and 42 has introduced new matter or concepts into the specification, as originally filed, thereby violating the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

Conclusion

22. No claim is allowed.

23. Applicant is advised that should claims 18 and 38-40 be found allowable, claims 43-46 will be objected to under 37 CFR § 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after

allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

24. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
November 17, 2006